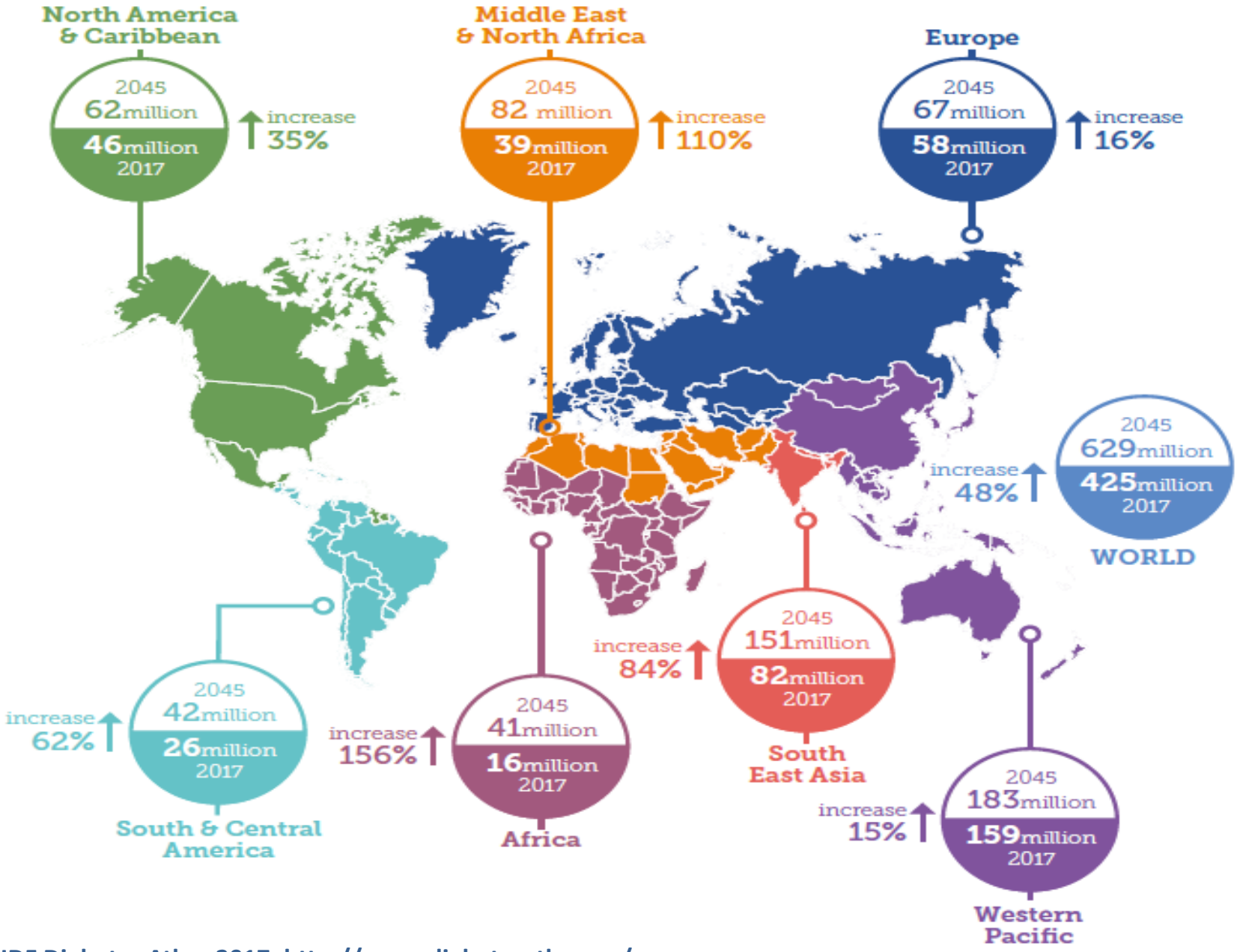
Immunological aspects in diabetes patients

Mihai G. Netea

Radboudumc

Diabetes increase between 2017 and 2045

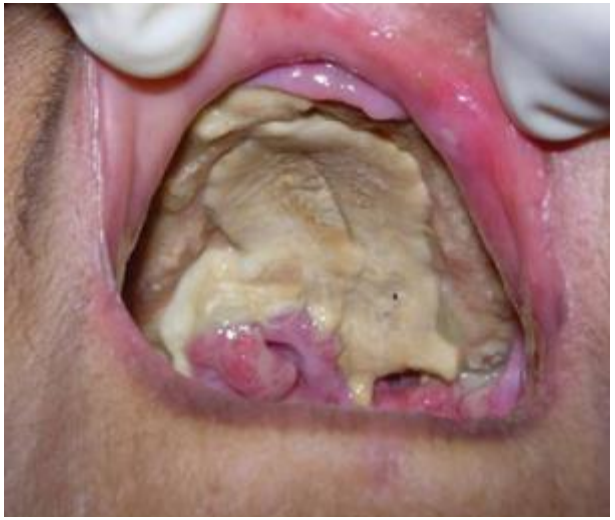


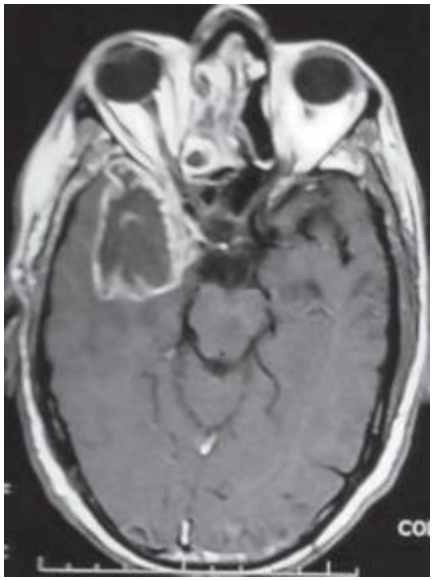
Source: IDF Diabetes Atlas, 2017; http://www.diabetesatlas.org/

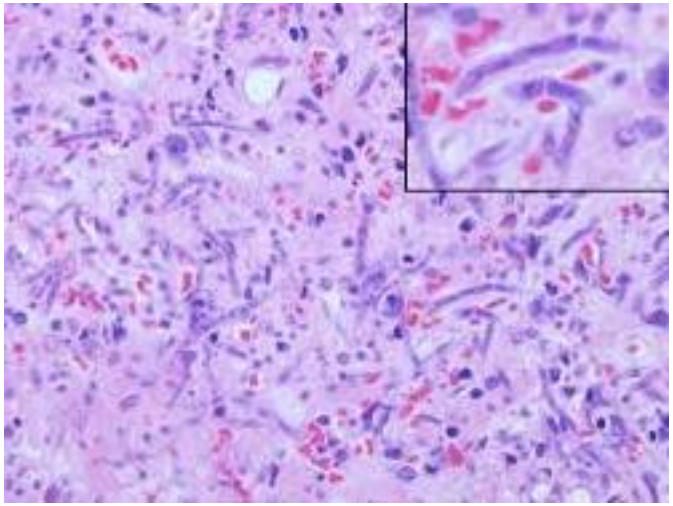
Are diabetes patients more susceptible to infections?

Some relatively rare infections almost exclusively in DM patients

Rhinocerebral mucormycosis (fungal infection)





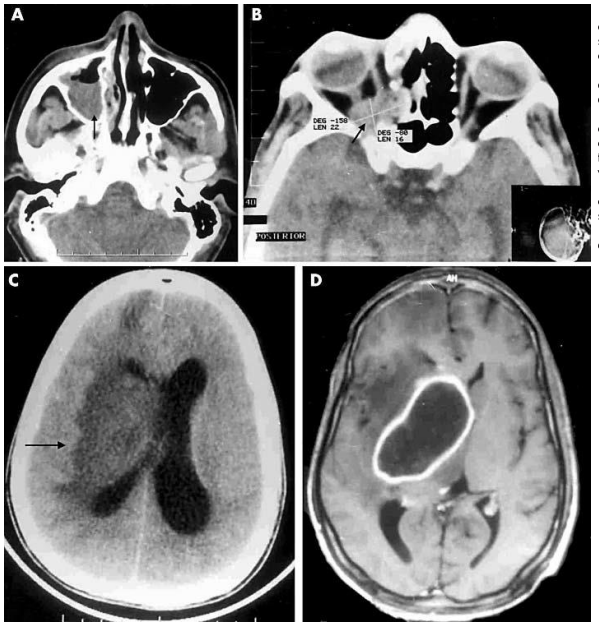


Hemotoxylin and Eosin stain
(necrosis, PMNs, hyphae)

Rhino-orbital mucormycosis emerging in tropics

India, 12 years diabetes,
dropped from care.
HbA1c 11%

Singh Bakshi,
Lancet DM 2016



Bhansali, PostGrad Med 2009

- India, Africa, Mexico
- Often first presentation of diabetes
- 6-fold increase in last 20 years
- Diagnostic & therapeutic challenge (e.g. no Amph B or surgery)
- High mortality
- Other invasive fungal infections also emerging (e.g. Aspergillus)

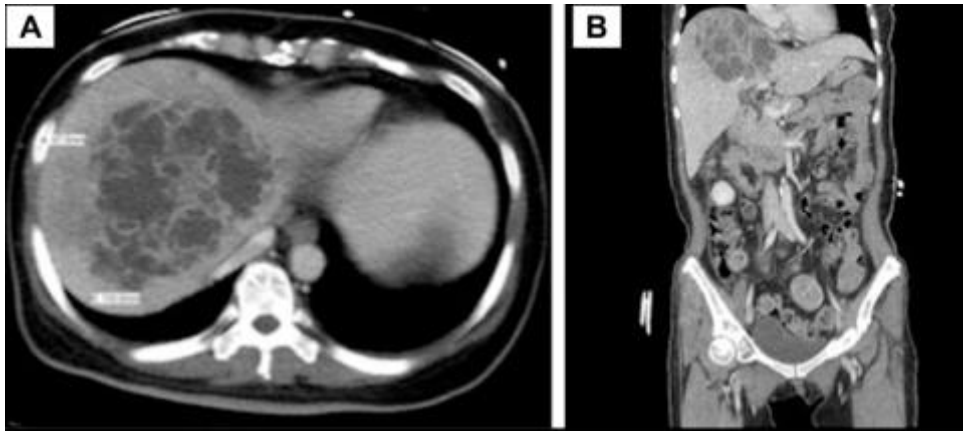
Other 'DM-specific' infections

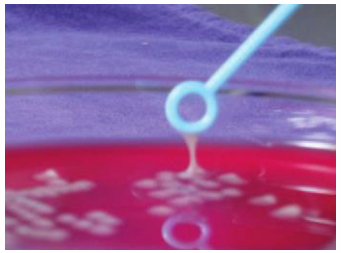
Klebsiella pneumoniae liver abscess: a new invasive syndrome

L Kristopher Siu, Kuo-Ming Yeh, Jung-Chung Lin, Chang-Phone Fung, Feng-Yee Chang

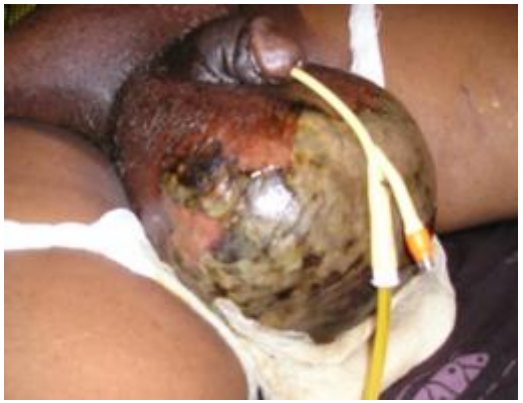
Klebsiella pneumoniae is a well known human nosocomial pathogen. Most community-acquired *K pneumoniae* infections cause pneumonia or urinary tract infections. During the past two decades, however, a distinct invasive syndrome that causes liver abscesses has been increasingly reported in Asia, and this syndrome is emerging as a global disease. In this Review, we summarise the clinical presentation and management as well the microbiological aspects of this invasive disease. Diabetes mellitus and two specific capsular types in the bacterium predispose a patient to the development of liver abscesses and the following metastatic complications: bacteraemia, meningitis, endophthalmitis, and necrotising fasciitis. For patients with this invasive syndrome, appropriate antimicrobial treatment combined with percutaneous drainage of liver abscesses increases their chances of survival. Rapid detection of the hypervirulent strain that causes this syndrome allows earlier diagnosis and treatment, thus minimising the occurrence of sequelae and improving clinical outcomes.

Extensive extra-hepatic lesions: CNS infections, necrotising fasciitis, endophtalmitis etc



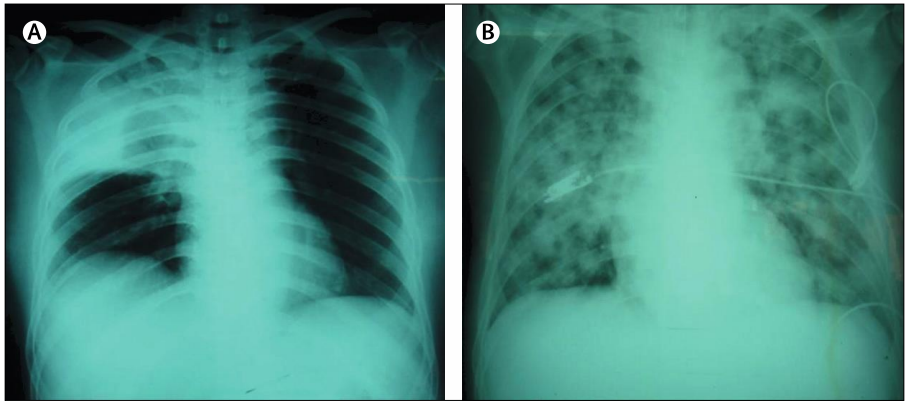


Specific capsular types
Loss of 'string test'



Fournier's gangrene

Mellioidosis



- Severe disease caused by *Burkholderia pseudomallei*
- Sepsis, pneumonia, abscesses
- Particularly in South-East Asia
- 40-60% of patients have DM

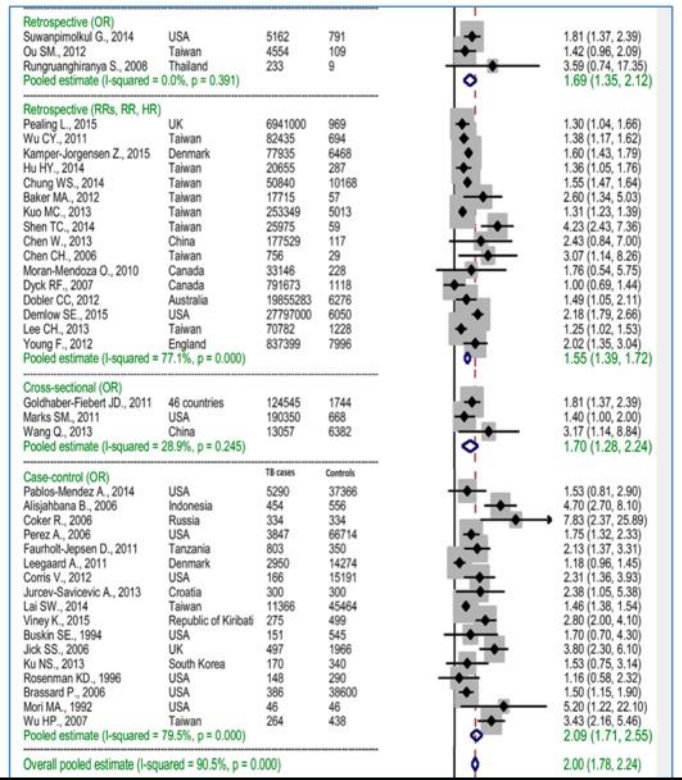
More common infections

- Candida (muco-cutaneous and invasive)
- Bacterial pneumonia
- Urinary tract infections
- Skin- and soft-tissue infections
- Eye infections
- Bloodstream infections (bacteremia)

- More common, often more severe
- More and longer hospital admission
- Increased risk of amputation after necrotising limb infections
- More metastatic infections (e.g. endophtalmitis in candidemia)

DM is associated with active TB

Author, year	Country	Population	TB cases	Estimate (95% CI)
Prospective (RR, HR)				
Cegielski JP., 2012	USA	14189	61	7.58 (2.94, 19.49)
Kim SJ., 1995	South Korea	814713	5105	4.97 (3.68, 6.70)
John GT., 2001	India	1251	166	2.24 (1.38, 3.65)
Leung CC., 2008	China	42116	326	2.69 (1.94, 3.72)
Pooled estimate (I-squared = 77.9%, p = 0.004)				3.59 (2.25, 5.73)



- 44 studies from 16 countries
- Prospective: DM ~ 3.6-fold higher TB risk (2.3-5.7)
- Higher in low-income and high-incidence
- Higher in Asia compared to Europe/USA
- Higher for confirmed TB and blood tested DM
- DM accounts for 11% (Nigeria) to 18% (India) of TB in high burden countries

Al-Rifai, Pearson, Critchley, Abu-Raddad. Plos One 2017

The impact of diabetes on tuberculosis treatment outcomes: A systematic review

Meghan A Baker[1,2], Anthony D Harries[3,4], Christie Y Jeon[5,10], Jessica E Hart[6], Anil Kapur[7], Knut Lönnroth[8], Salah-Eddine Ottmani[8], Sunali D Goonesekera[2] and Megan B Murray[2,9*]

	Relative risk	95% CI
2-mth culture +	Highly variable; no summary statistics	
Failure or death	1.69	1.36 - 2.12
Death	1.89	1.52 - 2.36
Recurrence	3.89	2.43 - 6.23

Baker et al, BMC Med 2011

Viral infections

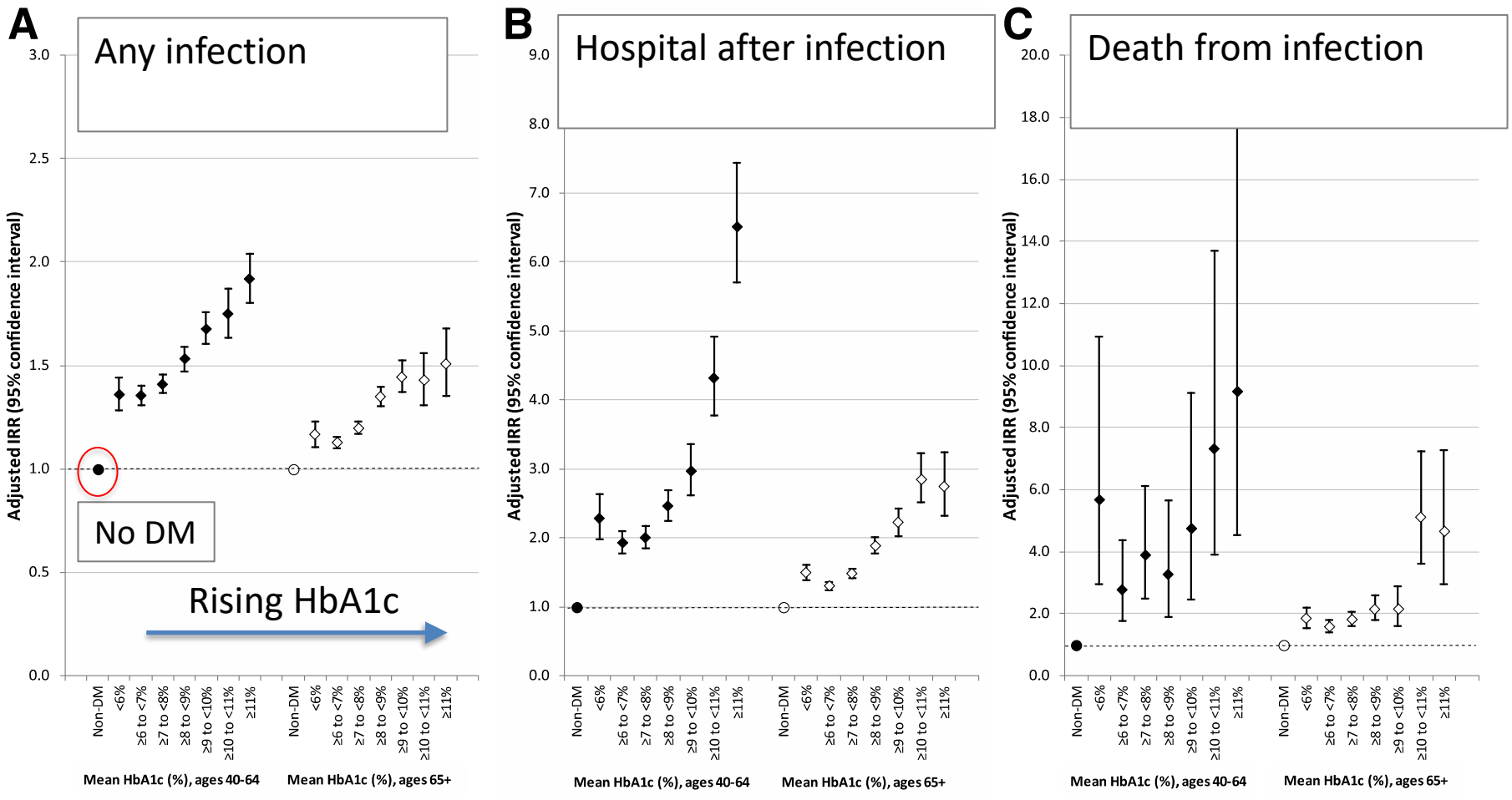
- Associations with DM for many viruses
- Influenza
- Emerging respiratory viruses
- Arboviruses (Dengue, West-Nile, Chikungunya, Zika, JE, yellow fever..)

- More and more severe
- SARS: 3-fold higher mortality among DM
- MERS: DM in 68% of cases and 66% of deaths
- Dengue: lower platelets, more ICU, higher mortality
- Chikungunya: more and longer myalgia/arthralgia

Diabetes and COVID-19

TABLE 1 | Overview of the risk of adverse COVID-19-related outcomes in patients with type 1 and type 2 diabetes mellitus.

	Study population	Number of patients (n)	Outcome	T1D *vs* no DM OR (95% CI)	T2D *vs* no DM OR (95% CI)
Barron et al. (9)	United Kingdom, nationwide population-based *March 1st – May 11th 2020*	T1D: 263,830 T2D: 2,864,670 No DM: 58,244,220	Mortality	3.51 (3.16 – 3.90)[#] 2.86 (2.58 – 3.18)[$]	2.03 (1.97 – 2.09)[#] 1.80 (1.75 – 1.86)[$]
McGurnaghan et al. (50)	Scotland, nationwide population-based *March 1st – July 31st 2020*	T1D: 34,383 T2D: 275,960 No DM: 5,143,951	Mortality and/or ICU admission	2.40 (1.82 – 3.16)[&]	1.37 (1.28 – 1.47)[&]
Gregory et al. (51, 52)[Φ]	Nashville, Tennessee, USA, single-center* *March 17th – December 24th 2020*	T1D: 136 T2D: 1,100 No DM: 19,422	Hospitalization	4.60 (3.04 – 6.98)[€]	3.42 (2.94 – 3.99)[€]



- English primary care data 2010-2015 (>85.000 DM patients, >150.000 controls)
- Consistently higher risk of infection compared to non-DM, higher risk with higher HbA1c
- 24% of TB among DM patients in UK is a result of poor glycemic control

Critchley J, Diabetes Care 2018

Conclusions 1

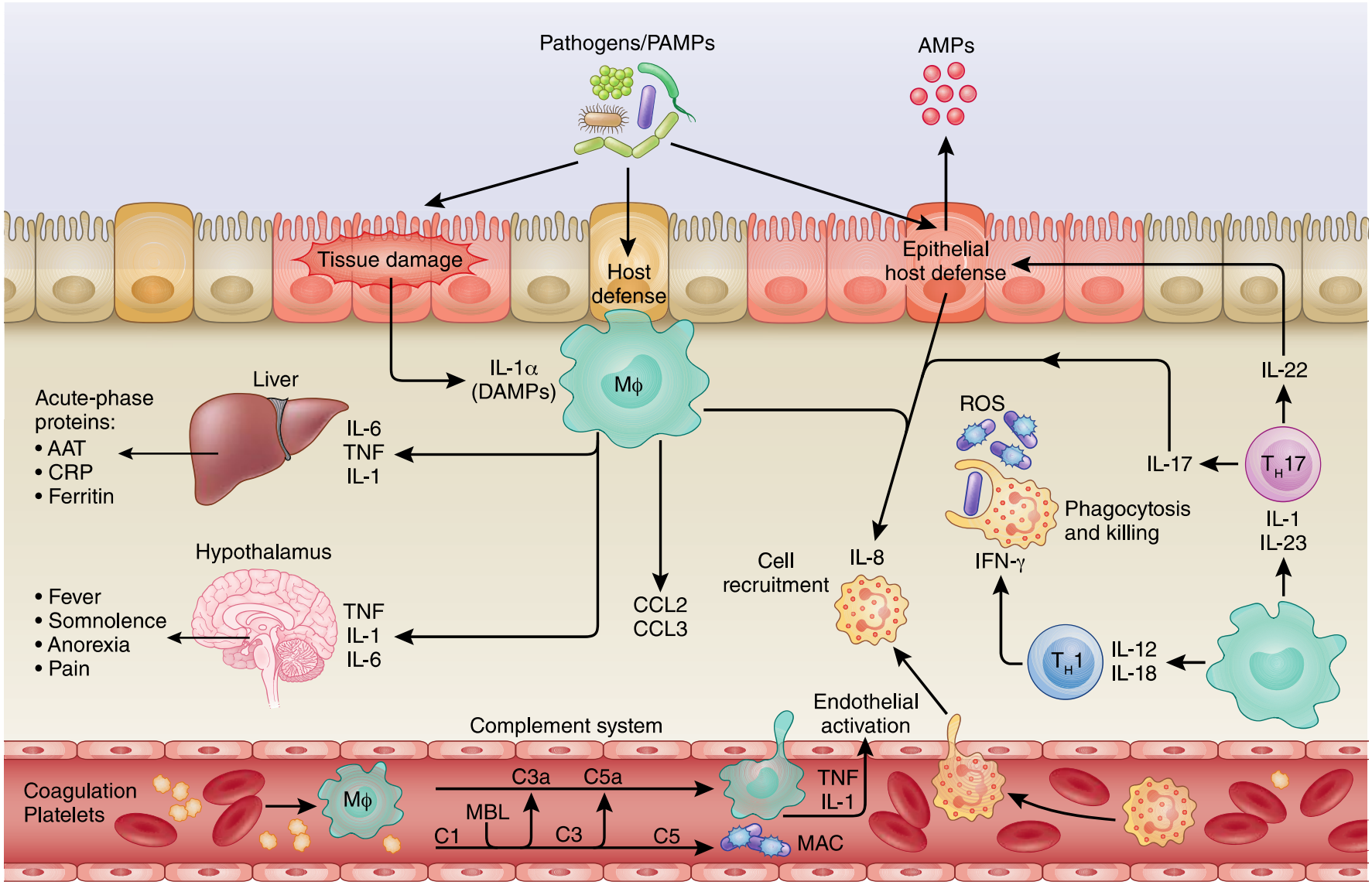
- Increase in diabetes prevalence worldwide
- Cardiovascular and other complications
- Infectious diseases
  - Higher risk (common, TB, viral, fungal, hospital-acquired…)
  - Worse outcome
- Highest risks associated with poor glycemic control

Contributing factors

- Host immunity
  - T-cells, B-cells, macrophages, neutrophils …
- Neuropathy, microangiopathy, wound healing
- Obesity
- More *Staphylococcus aureus* carriage
- Glycosuria
- More health-care associated infections
  - More hospitalization, more instrumentation

- poor glycemic control:
  - more infections, more admissions, higher mortality

Anti-microbial host defense



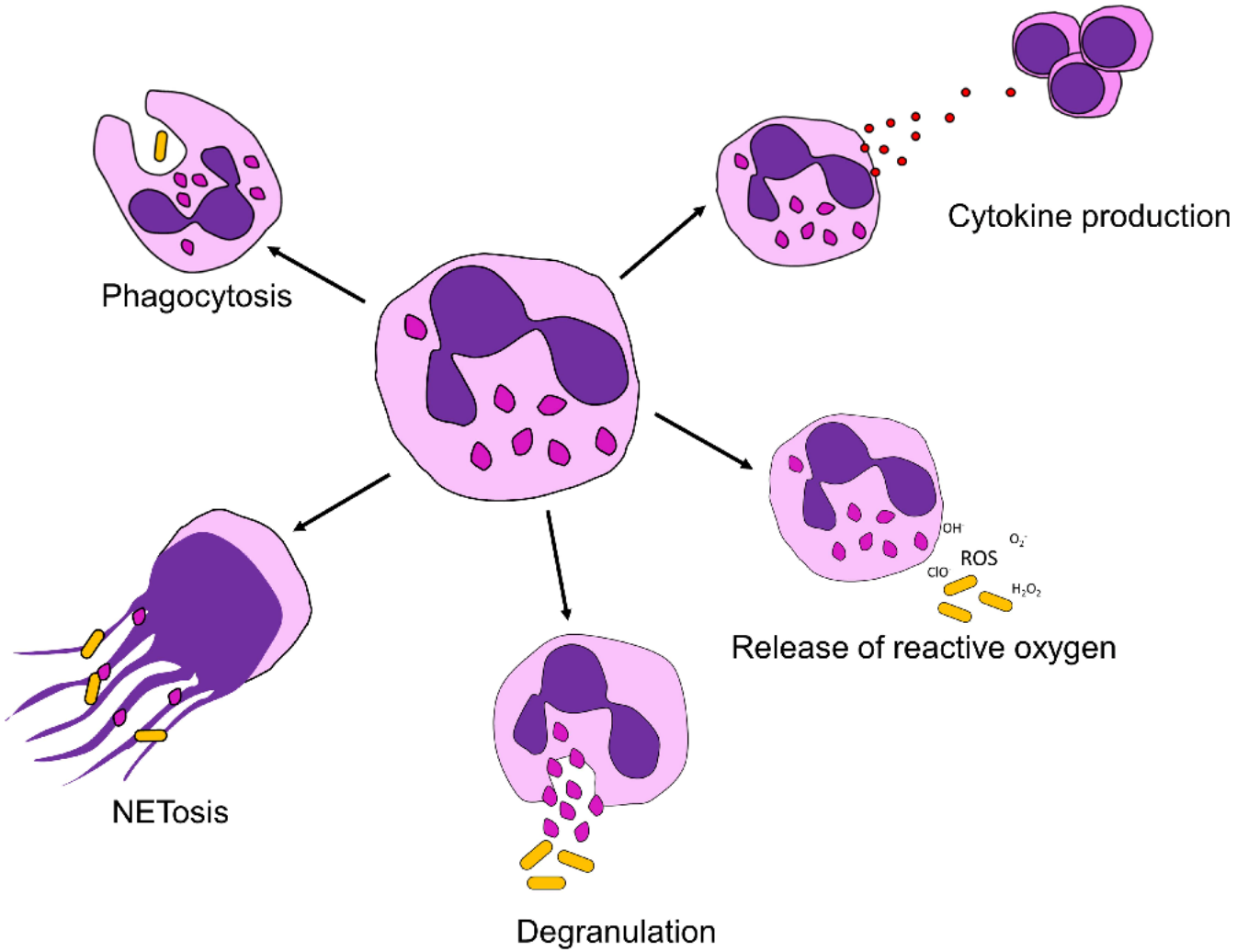
Netea et al, Nature Immunol 2017

Immune cell populations in type 1 diabetes

	50FG	300DM	p
Size (*n*)	53	227	
WBC (10^9/l)	14.45 (11.33, 18.55)	14.54 (11.80, 18.32)	0.548
Neutrophils (10^9/l)	0.22 (0.12, 0.41)	0.15 (0.09, 0.26)	0.009
Neutrophils (%)	1.30 (0.85, 3.00)	1.00 (0.60, 1.80)	0.009
Lymphocytes (10^9/l)	10.43 (7.52, 13.08)	10.27 (8.22, 12.79)	0.77
Lymphocytes (%)	72.90 (65.25, 76.95)	72.20 (66.70, 77.10)	0.946
Monocytes (10^9/l)	3.36 (2.79, 4.36)	3.70 (2.80, 4.83)	0.285
Monocytes (%)	24.60 (20.40, 31.40)	25.70 (20.90, 30.80)	0.526
Eosinophils (10^9/l)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.739
Eosinophils (%)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.949
Basophiles (10^9/l)	0.12 (0.09, 0.21)	0.12 (0.08, 0.17)	0.707
Basophiles (%)	0.90 (0.60, 1.20)	0.80 (0.60, 1.20)	0.479

Janssen et al, Metabolism 2021

Neutrophil biological activities



Blanter et al, J Inflamm Res

Neutrophil function in diabetes patients

TABLE 1 | Studies investigating neutrophil chemotaxis in diabetes.

Study	Animal model/human volunteer type	Chemotaxis phenotypes reported in diabetes
Studies reporting a decrease in neutrophil chemotaxis in T1D or T2D compared to control		
(48)	HVs + T2D volunteers	↓ in chemotaxis towards casein and human serum
(117)	HVs + 17 children with T1D	↓ chemotaxis towards *Staphylococcus epidermidis* & albumin
(118)	HVs + those with T2D (mild to severe periodontitis)	No difference between HVs and those with mild periodontitis+T2D. Significant ↓ in severe periodontitis + T2D. Endotoxin activated plasma and fMlp used as chemoattractant
(116)	Alloxan treated rat model	↓ in chemotaxis. Incubating healthy rat neutrophils in diabetic rat plasma also ↓ chemotaxis
(119)	HVs+ volunteers with T1D	↓ chemotaxis towards zymosan-activated plasma. No difference towards fMlp and *Escherichia coli* supernatant
(49)	HVs + people with T1D and T2D	↓ chemotaxis towards fMlp but no difference towards healthy control serum
(55)	Akita mouse (point mutation in Ins2 gene- inability to produce insulin-T1D model)	↓ chemotaxis towards fMlp and WKYMVm but no difference in random (unstimulated) migration.
(120)	Alloxan treated rats	No WT rats used in the study. ↓ chemotaxis towards casein and fMLP in rats with severe compared to mild diabetes
(121)	Neutrophils investigated from WT rats incubated in serum from Alloxan treated rats or WT	No difference in chemotaxis towards fMLP or Leukotriene B4. ↓ chemotaxis towards LPS-activated rat sera in diabetic serum group
(122)	HVs + people with T2D undergoing tooth extractions	↓ chemotaxis towards fMLP
(51)	HVs + people with insulin dependent diabetes	↓ chemotaxis towards fMLP
(123)	Low dose STZ-treated mice	↓ chemotaxis towards casein

Dowey et al, Front Immunol 2021

Neutrophil function in diabetes patients

TABLE 2 | Studies Investigating Neutrophil ROS production in Diabetes.

Study	Animal model/human volunteer type	Changes in neutrophil ROS production reported in diabetes group compared to healthy control
Studies investigating neutrophil extracellular ROS production		
(54)	HVs + people with T2D	↑ in response to PMA and zymosan
(136)	HVs + people with T2D	↑ in response to PMA ↓ in response to zymosan
(137)	HVs + PWD (does not specify type)	No difference in response to PMA
(138)	HVs + people with T1D	↑ in unstimulated neutrophils. ↓ in response to fMLP and no difference when using PMA
(55)	Akita mouse (point mutation in Ins2 gene- inability to produce insulin-T1D model)	↑ in response to fMLP
(139)	HVs+ well controlled T1D	No difference in response to PMA
(140)	HVs+ volunteers with poor, moderate or well controlled T1D or T2D	↑ in response to fMLP in poorly controlled diabetes only (>8% HbA1c)
(123)	Low dose STZ-treated mice vs. WT	↓ in response to PMA
(141)	Healthy cats vs. diabetic cats (partial pancreatectomy)	↑ in response to PMA
(142)	HVs + patients with diabetes (T1D or T2D)	↑ in unstimulated neutrophils but decreased in response to PMA and zymosan
(143)	HVs + people with poorly controlled T2D	↓ in response to a mixture of zymosan, phorbol and NaF
(144)	HVs + patients with odontogenic bacterial infections or oral candidiasis with or without diabetes	↓ in response to PMA
(59)	HVs+ people with T1D or T2D with and without varying severities of periodontitis	↑ ROS in response to PMA and fMLP in participants with moderate (7-8%) or poor (>8%) glucose control
(145)	HVs + people with DFD	↓ in ROS in response fMLP. G-CSF increased ROS.
Studies investigating neutrophil intracellular ROS production		
(122)	HVs + people with T2D undergoing tooth extractions	↓ in ROS (stimulus not reported)
(146)	HVs + people with T2D and varying stages of diabetic nephropathy	↑ ROS. Greatest increase in patients with stage 4 nephropathy. (Multiple stimuli employed)
(147)	Newly diagnosed T1D patients not yet undergoing insulin therapy, T1D patients with disease duration of >3 months and healthy controls	↓ in ROS in response to PMA (greatest decrease in patients without insulin therapy)
(148)	HVs + people with T1D or T2D	↓ in ROS in response to PMA. Tolrestat increased ROS
(149)	HVs + infection free people with poorly controlled T2D (HbA1C <7.5%)	↓ in ROS in response to PMA
(126)	HVs + people with T2D and periodontitis	No difference in response to PMA. ↓ in response to zymosan
(150)	STZ-treated rats v.s WT rats	↑ ROS at basal level (no stimulus used)
(125)	HVs + people with diabetes and periodontal disease	No difference in response to PMA. ↓ in response to zymosan
(49)	HVs + People with T1D or T2D	No difference in response to PMA
(151)	HVs + people with T1D or T2D	↓ in response to endotoxin activated plasma
(141)	Healthy cats & diabetic cats (partial pancreatectomy)	No difference in response to PMA

Dowey et al, Front Immunol 2021

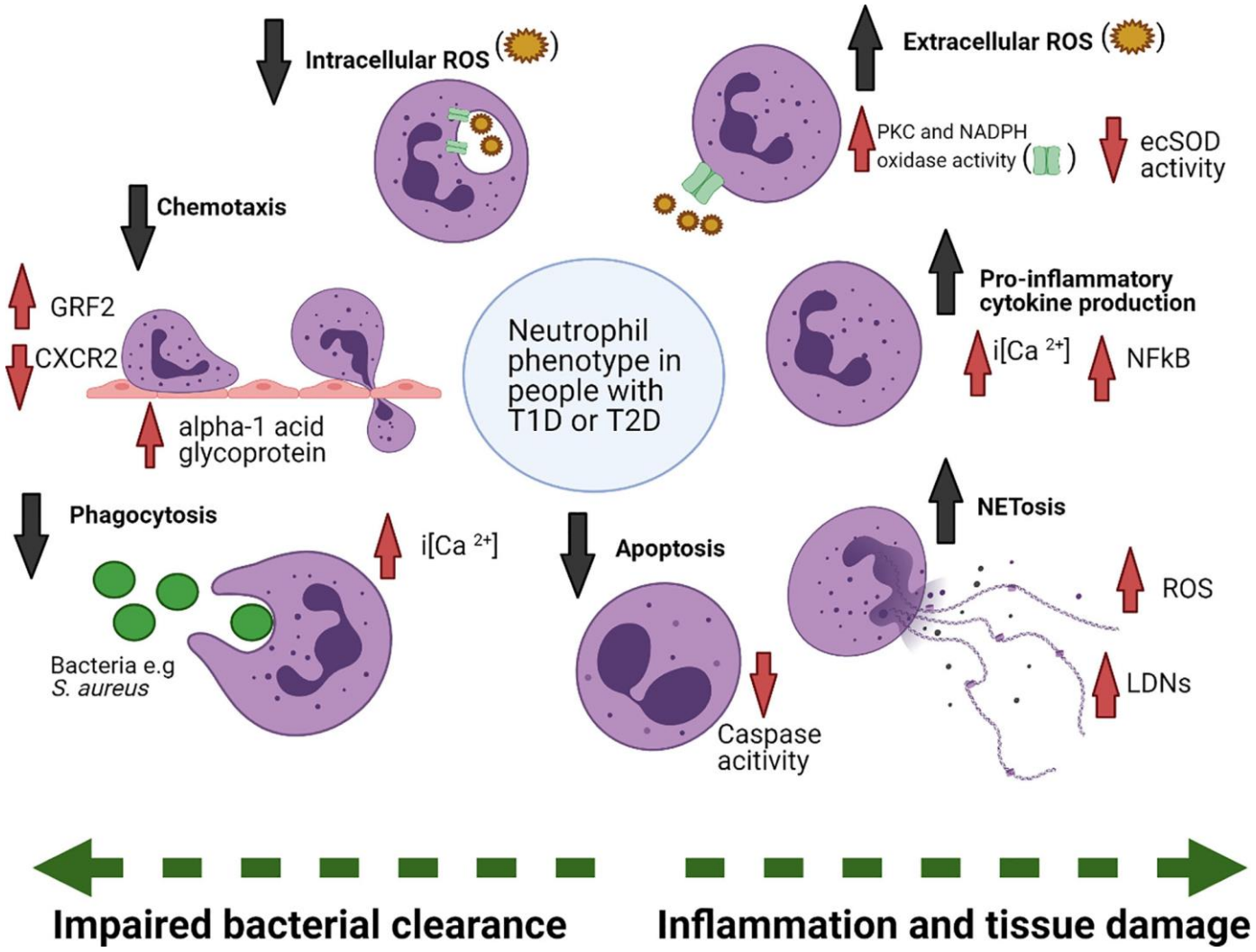
Neutrophil function in diabetes patients

TABLE 3 | Studies investigating neutrophil phagocytosis in diabetes.

Study	Animal model/human volunteer type	Phagocytosis phenotypes reported in diabetes
Studies reporting a decrease in neutrophil phagocytosis in diabetes compared to control		
(258)	HVs + peoplewith T2D	↓ in phagocytosis of *S. aureus*- only acidotic diabetic group, no difference in people with non-acidotic diabetes
(50)	Alloxan treated rat model	↓ in phagocytosis of *Streptococcus pneumoniae*
(259)	HVs + children with T1D	↓ in phagocytosis
(260)	HVs + T2D	↓ in phagocytosis of *S. aureus* but no difference in phagocytosis of *S. epidermidis*
(261)	HVs + people with T2D	↓ in phagocytosis of *Burkholderia pseudomallei*
(262)	Alloxan and diet induced diabetic mice	↓ in phagocytosis of LPS-coated fluorescent beads
(190)	Alloxan treated rats- peritoneal neutrophils	↓ in phagocytosis of opsonised *Candida albicans*
(65)	Abdominal sepsis model in diabetic diet induced mice	↓ in phagocytosis of *Escherichia coli*
(263)	HVs + people with T2D and poorly controlled blood glucose (>120 mg/dL)	↓ in phagocytosis of oil droplets containing oil red O, coated with *E. coli* derived LPS
(264)	HVs + people with T2D	↓ in phagocytosis of opsonised oil droplets containing oil red O, coated with *E. coli* derived LPS
(123)	Low dose STZ-treated mice	↓ in phagocytosis of zymosan
(265)	WT mice v.s db/db mice	↓ in phagocytosis of pHrodo Red *S. aureus* Bioparticles Conjugate
(150)	STZ-treated rats v.s WT rats	↓ in phagocytosis of opsonised and unopsonised *Saccharomyces cerevisiae*
(147)	Newly diagnosed T1D patients not yet on insulin therapy, T1D patients with disease duration of >3 months and healthy controls	↓ in phagocytosis of *E. coli* (greatest decrease in new diagnosed patients, not undergoing insulin therapy)
(122)	HVs + people with T2D undergoing tooth extractions	↓ in phagocytosis of FITC- labelled opsonised *E.coli*
(266)	HVs + people with diabetes controlled with insulin	↓ in phagocytosis *Candida guilliermondii*
(139)	HVs + people with well-controlled T1D	↓ in phagocytosis *Candida albicans*
(267)	HVs + people with T2D	↓ in phagocytosis- only in K1/K2 *Klebsiella pneumoniae* no difference in non-K1/K2 serotypes
(151)	HVs + people with T1D or T2D	↓ in phagocytosis of heat killed opsonised *Candida albicans*
(154)	HVs + people with T1D or T2D all receiving insulin	↓ in phagocytosis of *S. aureus*
(144)	HVs + patients with odontogenic bacterial infections or oral candidiasis with or without diabetes	↓ in phagocytosis of latex particles

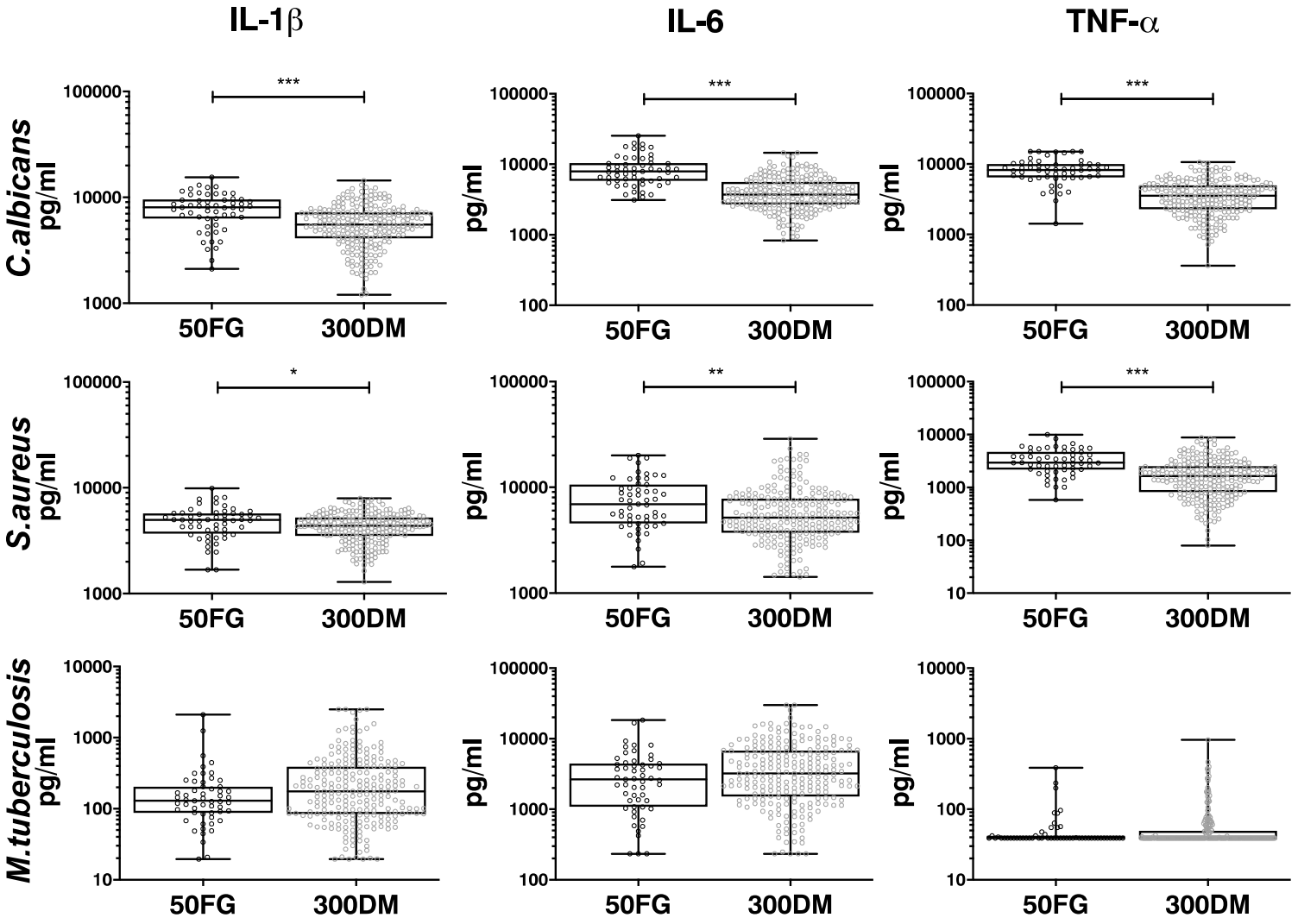
Dowey et al, Front Immunol 2021

Neutrophil function in diabetes patients



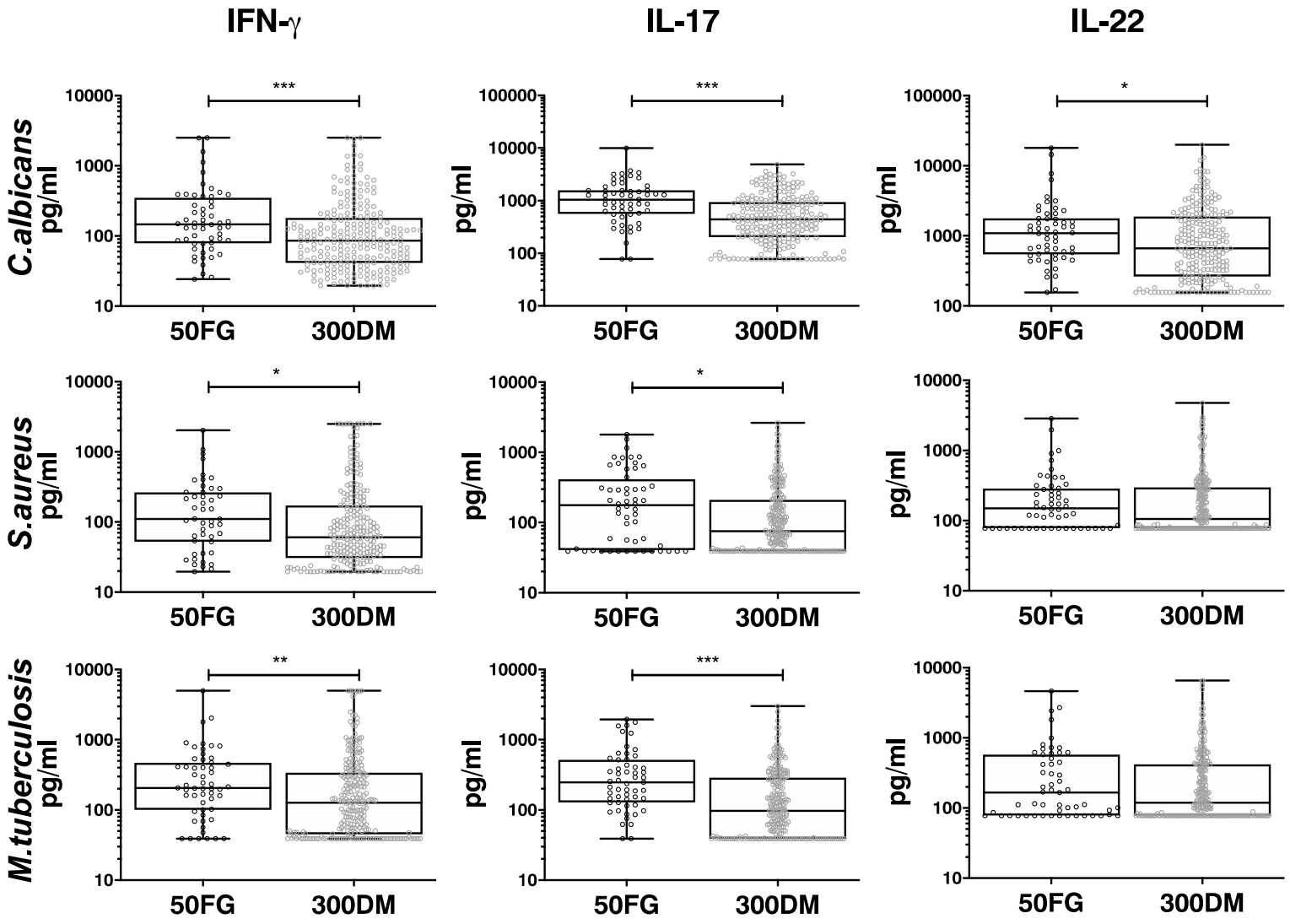
Dowey et al, Front Immunol 2021

Monocyte cell function in diabetes



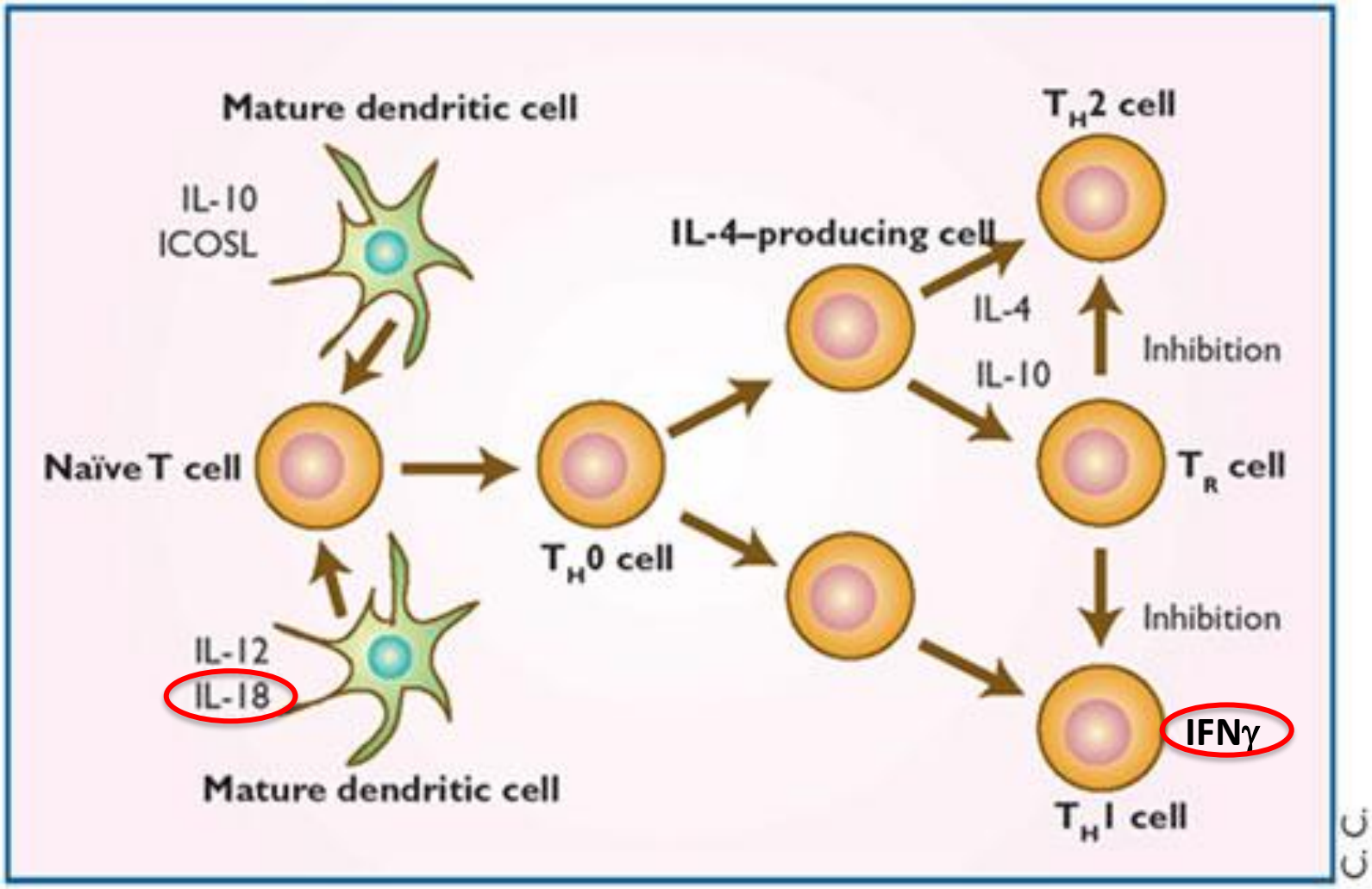
Janssen et al, Metabolism 2021

T-helper cell function in diabetes



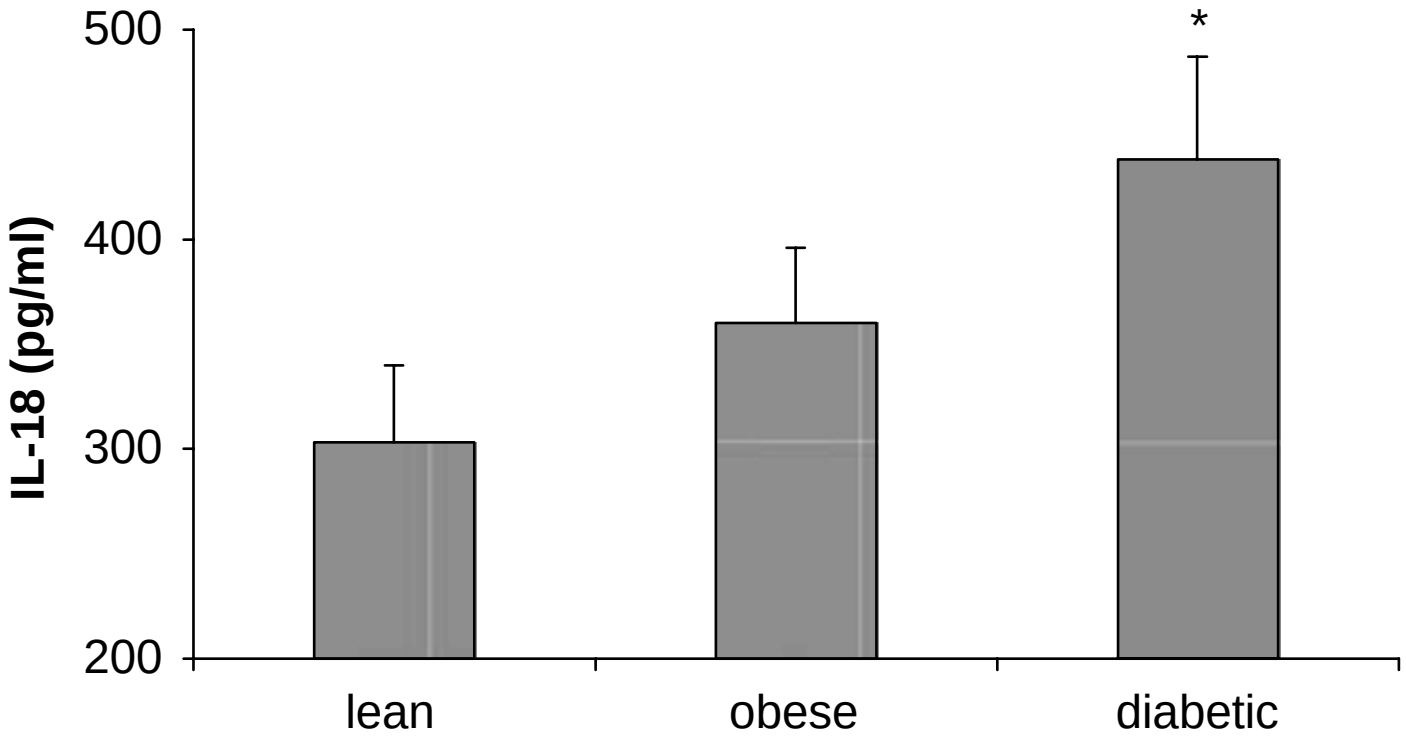
Janssen et al, Metabolism 2021

IL-18 is crucial for IFNγ production



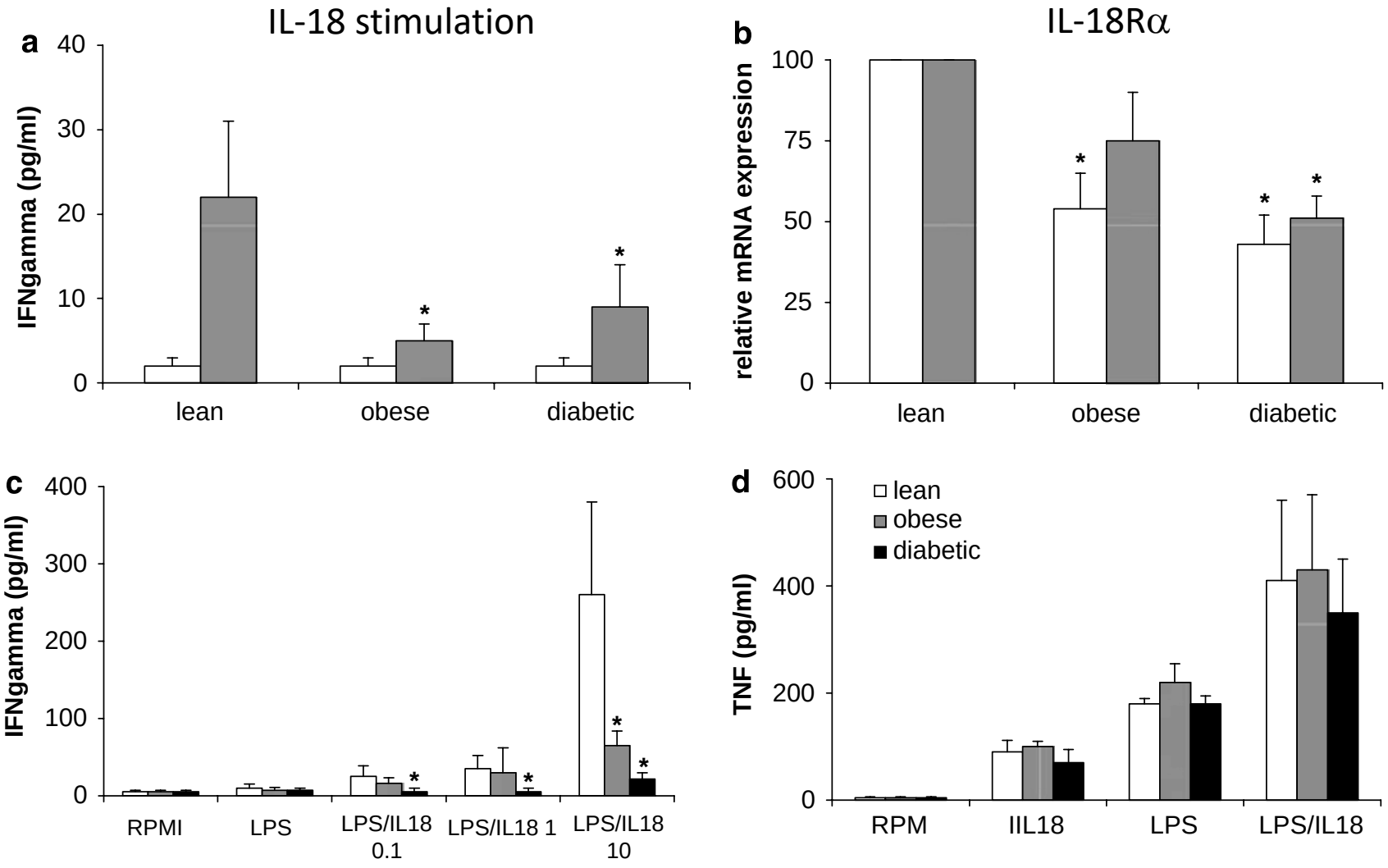
Umetsu et al, Nature Immunol

IL-18 in diabetes patients



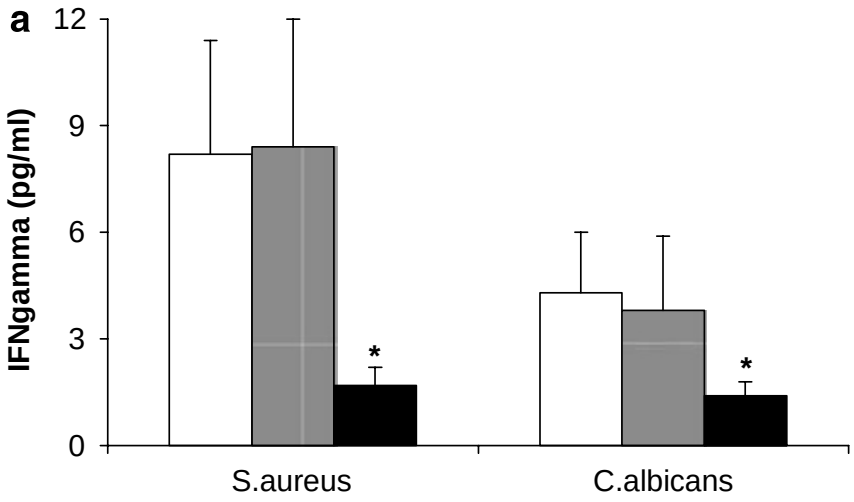
Zilverschoon et al, Int J Obesity

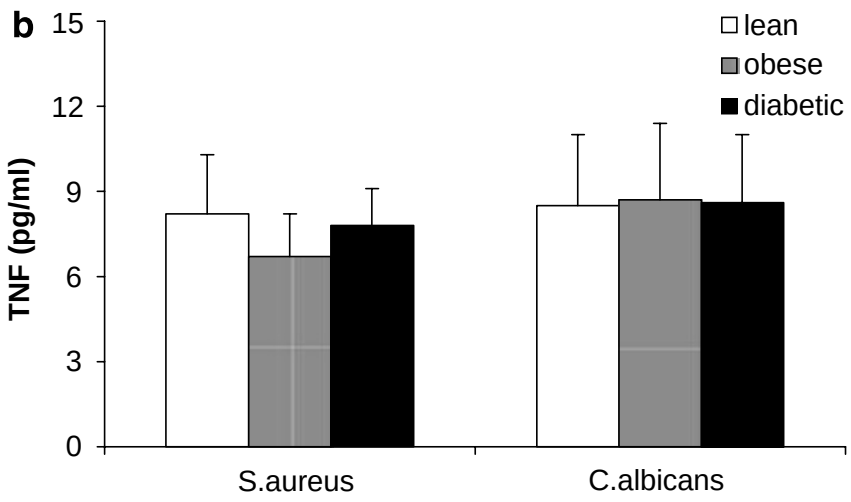
IL-18 resistance in diabetes patients



Zilverschoon et al, Int J Obesity

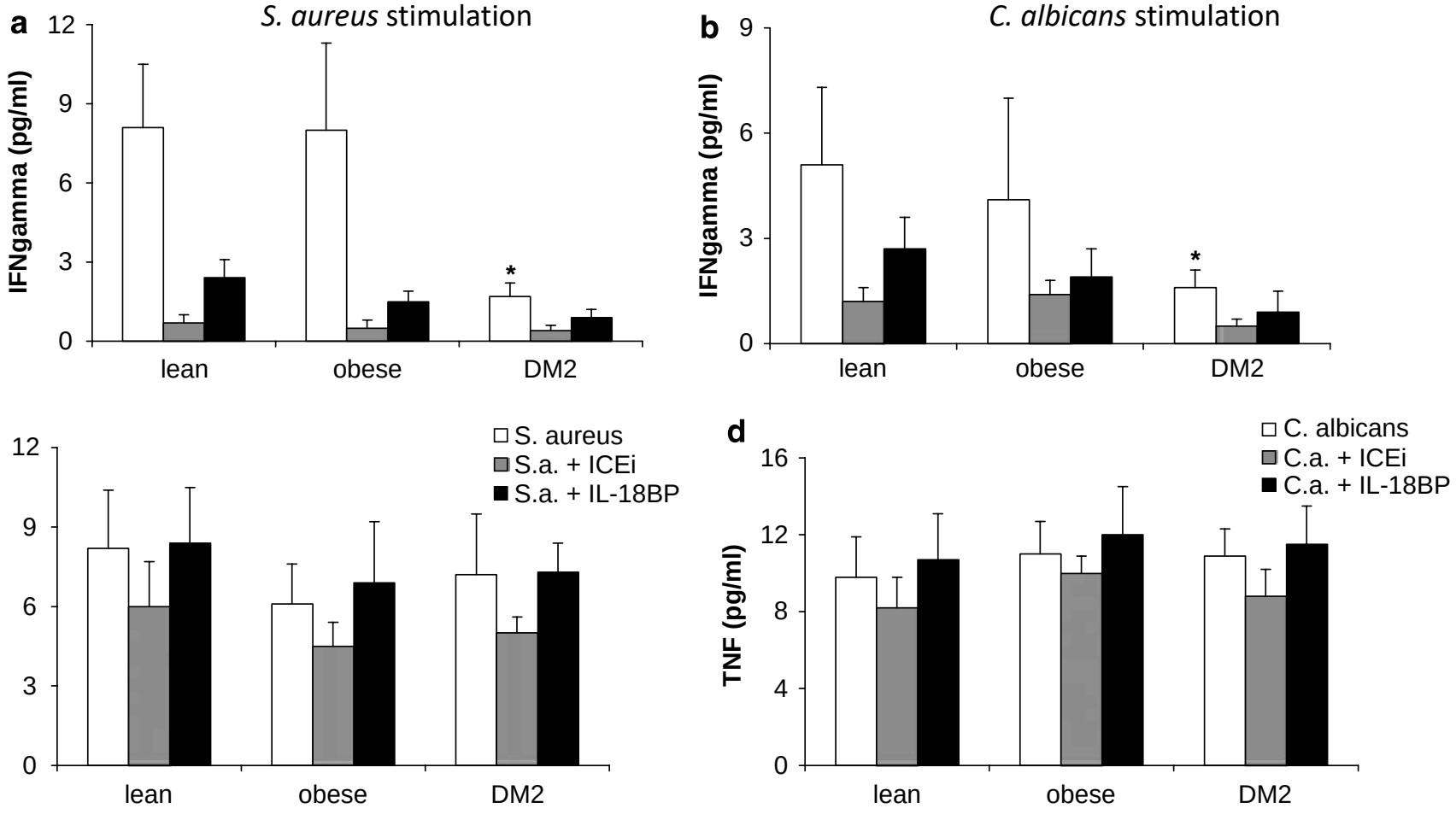
IFNγ production in diabetes patients is defective





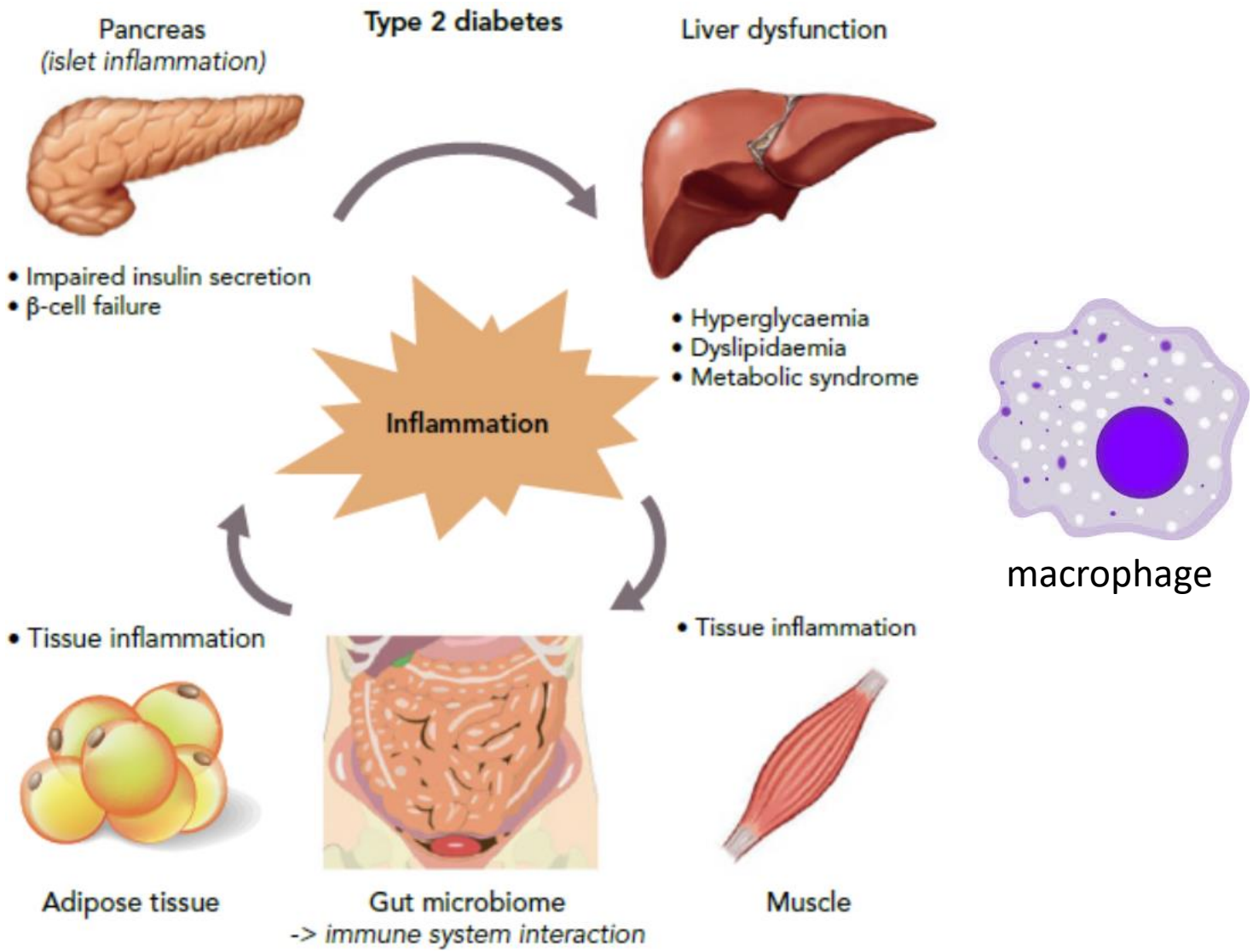
Zilverschoon et al, Int J Obesity

IFNγ production in diabetes patients is IL-18 dependent



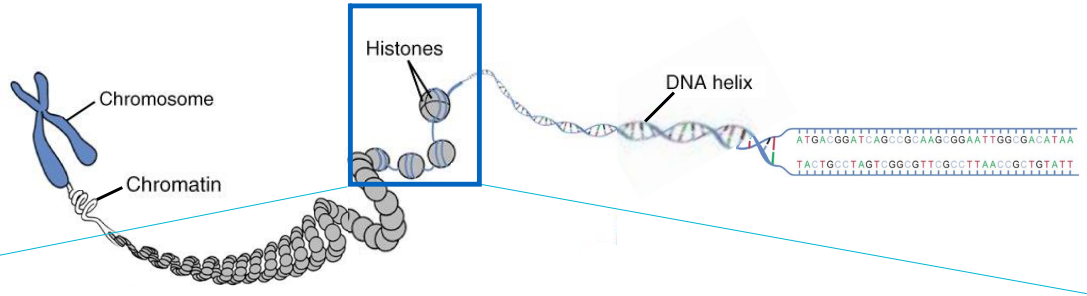
Zilverschoon et al, Int J Obesity

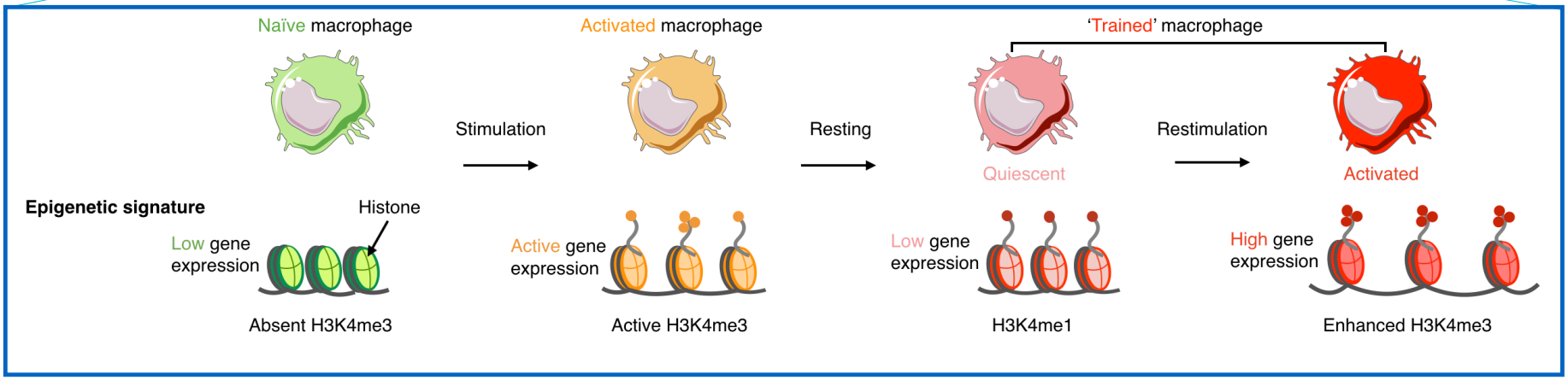
Inflammation in diabetes patients



Tsalamandris et al, Int Soc Cardiovasc Pharm

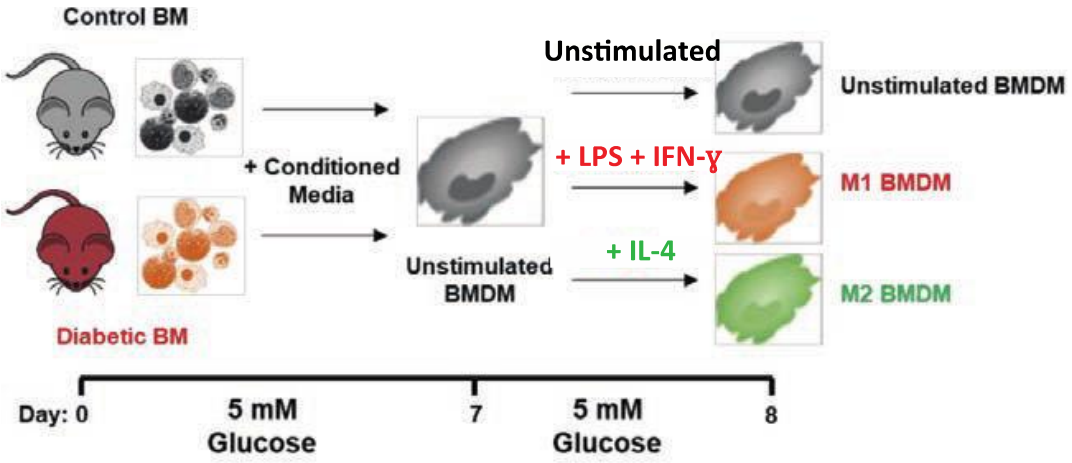
Long-term epigenetic reprogramming in myeloid cells

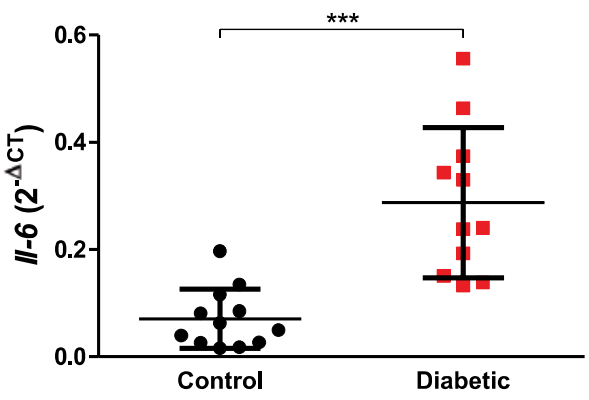


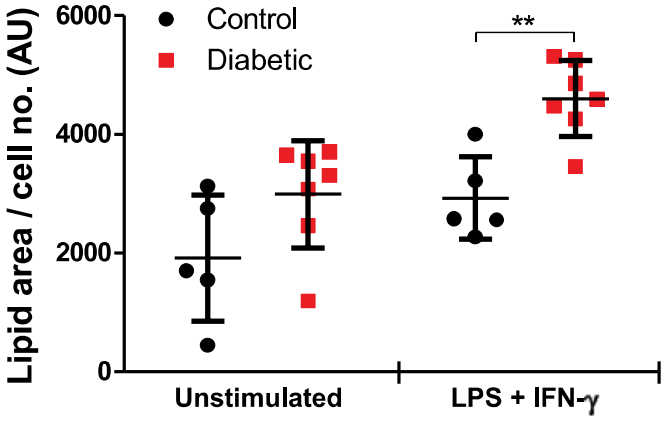


Resting | **Infection** | **Resting** | **Re-infection**

Bone marrow-derived macrophages maintain hyperglycemic memory

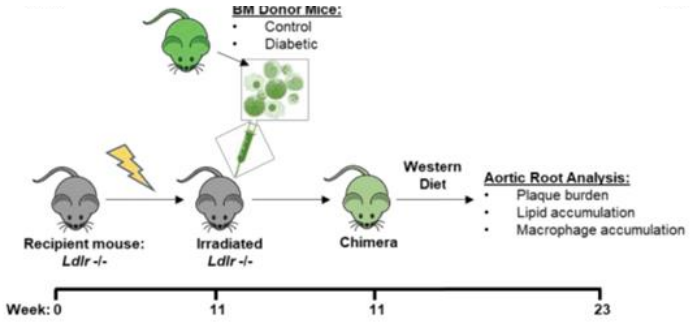


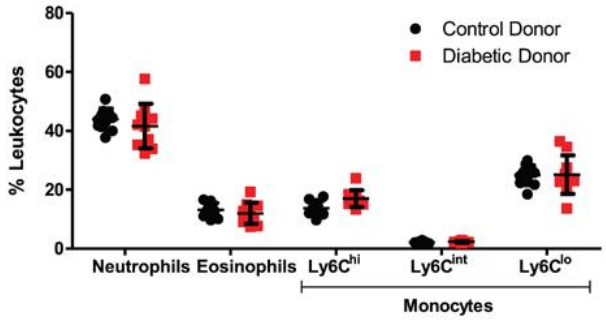


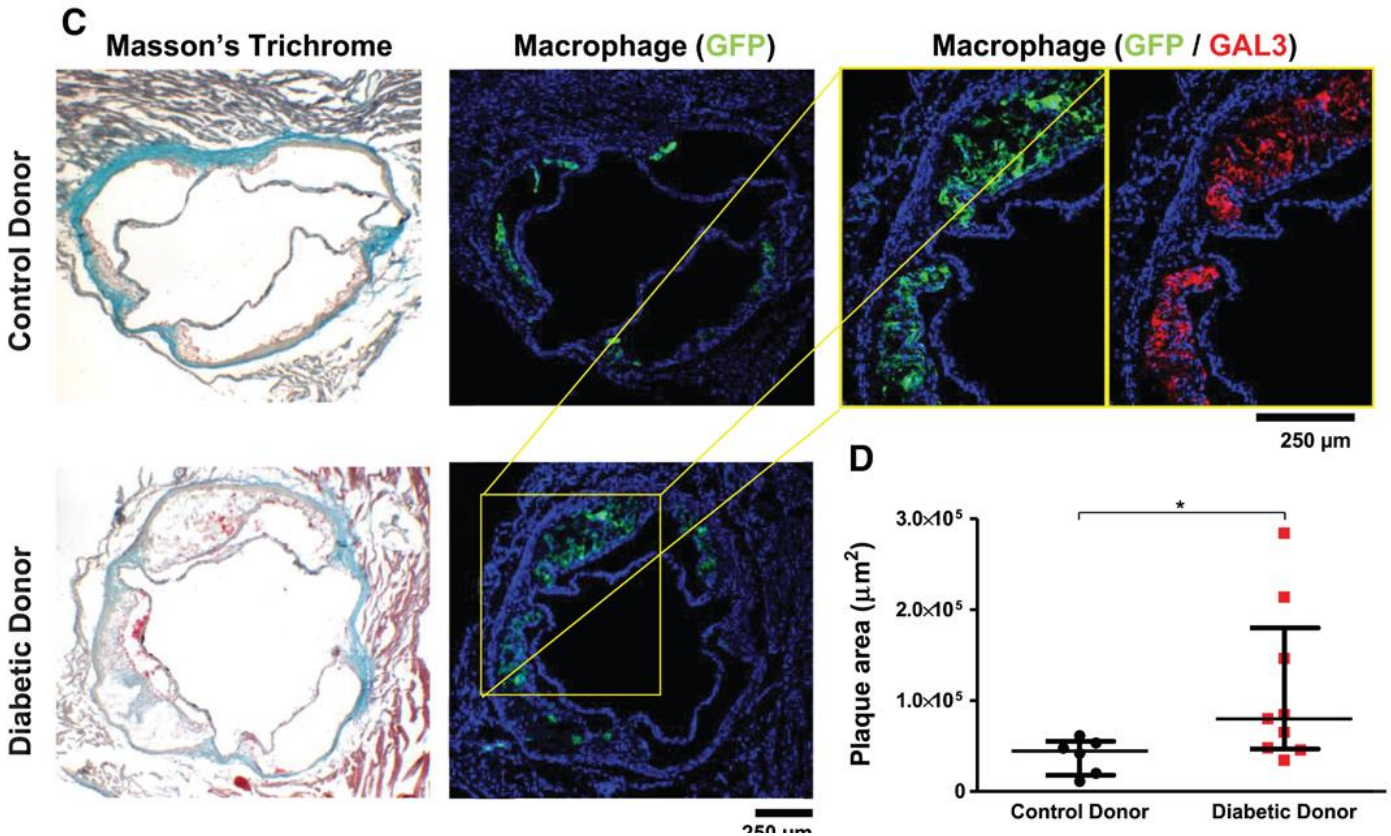


Edgar et al, Circulation 2021

Bone marrow-derived macrophages from diabetic mice drive atherosclerosis







Edgar et al, Circulation 2021

Conclusions 2

- Diabetes patients present both increased susceptibility to infections and increased vascular complications
- Immune cells of diabetes patients display a defective response to pathogens
  - Decreased neutrophil and monocyte function
  - Defective IFNg responses due to IL-18 resistance
- At the same time, diabetes patients show inappropriate systemic inflammation
  - Role of epigenetic and functional changes due to hyperglycemia in myeloid cells and their progenitors in the bone marrow

Thank you !

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